

REMARKS

I. Status of the Application and Claims

The Office has advised Applicants that the Amendment dated October 5, 1999, has been entered. (See Advisory Action (Paper No. 17), page 1.) Accordingly, claims 27, 34-36, 38, 40, 41, and 48-50 are pending in the application. All claims have been rejected.

II. Claims 36-38 Particularly Point Out and Distinctly Claim Applicants' Invention

Claims 36-38 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for particularly pointing out and distinctly claiming the subject matter that Applicants regard as their invention. (Office action mailed April 5, 1999, page 8.) Specifically, the Office contends that the terms "E1A," "MLP," "CMV," and "RSV-LTR" are vague since an abbreviation may have more than one meaning. (Office action mailed August 31, 1998, page 10.) As to claim 37, the rejection is moot in view of its cancellation by Applicants. Applicants traverse the rejection as to claims 36 and 38 for the reasons of record, and the following reasons.

At the outset, Applicants respectfully point out that as to three of the four disputed terms the rejection is in direct conflict with the Office's own understanding of their meaning. As stated by the Office, "[t]he arguments concerning CMV, MLP and RSV-LTR are convincing that one of skill in the art would know what these undefined abbreviations would mean in the context of the claimed invention." (Office action mailed August 31, 1998, page 5.) The meaning of a term cannot be known to one of

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skill in the art and vague as well. Withdrawal of the rejection with respect to these terms is appropriate.

The words in a claim must be read in light of the specification. M.P.E.P. § 2111, *citing In re Prater*, 162 U.S.P.Q. 541, 550-51 (C.C.P.A. 1969). When claim 36 is read in light of Applicants' specification, it is evident that one of skill in the art would understand the meaning of "E1A," as well as the meaning of the other three terms.

These terms do not appear in a vacuum. They are part of a specification providing ample guidance for their interpretation. See *Renishaw PLC v. Marposs Societa' Per Azioni*, 48 U.S.P.Q.2d 1117, 1123 (Fed. Cir. 1998). "E1A," for example, is used in the context of "the adenovirus E1 regions." (Specification, page 20.) In view of this linkage between "E1A" and adenoviruses, one of skill in the art would understand that the promoter recited in claim 36 is the adenovirus E1A promoter.

It is also evident from the references cited by the Office that one of skill in the art would understand the meaning of "E1A." PCT application WO 94/08026 to Kahn *et al.* ("Kahn") discusses promoters useful for expressing heterologous genes in recombinant adenovirus. According to Kahn, a "promoter that may be used consists of the early promoter of the E1a region of the adenovirus." (Kahn, page 4, lines 20 and 21.)

In addition, Kahn also provides evidence that the meanings of "MLP," "CMV," and "RSV-LTR" are understood by the skilled artisan. Kahn states that "[a] particularly preferred endogenous promoter is the major late strong promoter (MLP) of the human adenovirus type 2." (*Id.*, lines 18 and 19.) Furthermore, Kahn describes "a promoter of

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. . . Cytomegalovirus (CMV)" and " a promoter contained in the LTR (Long Terminal Repeat) of the Rous Sarcoma Virus (RSV)" (*Id.*, lines 27-29.)

Words in a claim must be given their ordinary and accustomed meaning.

Johnson Worldwide Assoc., Inc. v. Zebco Corp., 50 U.S.P.Q.2d 1607, 1610 (Fed. Cir. 1999). The evidence of record confirms that the disputed terms have an ordinary and accustomed meaning to one of skill in the art. Accordingly, they cannot be ambiguous. In view of the remarks, Applicants request reconsideration and withdrawal of this rejection.

III. The Claims Are Patentable Over the Art

A. Claims 27, 28, 30, 31, 34-39, 41, and 48-50 Are Patentable Over Kahn in View of Mullenbach

Claims 27, 28, 30, 31, 34-39, 41, and 48-50 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Kahn in view of Mullenbach *et al.*, UCLA Symp. Mol. Cell. Biol., New Ser., v. 82, pp. 313-326 (1988).¹⁴ (Office action, page 8.)

Applicants traverse the rejection for the reasons of record, supplemented as follows.

Kahn is cited as teaching replication-defective recombinant adenoviral vectors for transfer of heterologous sequences into cells of the central nervous system and cells transfected with the vectors. (Office action mailed January 21, 1998, page 19.) This reference is also cited as disclosing that these vectors are useful for study and regulation of cloned genes for therapy involving production of a protein of interest. (*Id.*) The Office admits that Kahn "does not teach glutathione peroxidase as a desired

¹⁴The rejection is moot as to claims 28, 30, 31, and 37, which have been canceled.

protein, whose encoding DNA could be incorporated into the disclosed adenoviral vectors. (*Id.*, page 20.)

The Office cites Mullenbach as teaching "the cDNA sequences of both a bovine and human glutathione peroxidase . . . and illustrate that glutathione peroxidase is a protein of interest." (*Id.*)

In view of this asserted teaching, the Office concludes that it would have been obvious to one of ordinary skill in the art at the time of the invention "to incorporate cDNA encoding a human or bovine glutathione peroxidase, taught by Mullenbach et al., into the adenoviral vectors and subsequently infected cells taught by Kahn et al. with a reasonable expectation of success as only routine techniques would be required, and for the express reason that Kahn et al. taught that the vectors were useful for recombinant expression of a protein of interest and Mullenbach et al. illustrate that glutathione peroxidase is a protein of interest."

Applicants submit that the rejected claims would not have been *prima facie* obvious to one of ordinary skill in the art as suggested by the Office. To establish a *prima facie* case of obviousness in view of a combination of references there must be some teaching, suggestion, or motivation, either in the references themselves, or in the knowledge of those skilled in the art, to combine them. Here, the Office has not provided a clear and convincing showing of how the references would have motivated one of ordinary skill in the art to combine their teachings to arrive at the claimed invention. *In re Dembicza*k, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999).

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In *Dembiczak*, the court reversed the Board of Patent Appeal and Interferences, holding that claims directed to trash bags resembling jack-o-lanterns were not obvious in view of a combination of references. Before addressing the merits of the case, the court discussed in great detail the showing required to establish a *prima facie* case of obviousness:

Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. . . .

We have noted that evidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved, although "the suggestion more often comes from the teachings of the pertinent references. . . ." **The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence."**

Id. at 1617 (citations omitted; emphasis added). The court then addressed the reasoning underlying the Board's (and examiner's) decision, finding it inadequate:

To justify this combination, the Board simply stated that "the Holiday and Shapiro references would have suggested the application of . . . facial indicia to the prior art plastic trash bags. However, rather than pointing to specific information in Holiday or Shapiro that suggest the combination with the conventional bags, the Board instead described in detail the similarities between the Holiday and Shapiro references and the claimed invention, noting that one reference or the other--in combination with each other and the conventional trash bags--described all of the limitations of the pending claims. **Nowhere does the Board particularly identify any suggestion, teaching or motivation to combine the children's art references (Holiday and Shapiro) with the conventional trash or lawn bag references, nor does the Board make specific--or even inferential--findings concerning the identification of the relevant art,**

the level of ordinary skill in the art, the nature of the problem to be solved, or any other factual findings that might serve to support a proper obviousness analysis.

To the contrary, the obviousness analysis in the Board's decision is limited to a discussion of the ways that the multiple prior art references can be combined to read on the claimed invention. . . . Yet this reference-by-reference, limitation-by-limitation analysis fails to demonstrate how the Holiday and Shapiro references teach or suggest their combination with conventional trash or lawn bags to yield the claimed invention.

Id. at 1617-18 (emphasis added.) In making the instant rejection, the Examiner has performed exactly the same reference-by-reference, limitation-by-limitation analysis faulted in *Dembiczak*.

This is evident from page 20 of the Office action mailed January 21, 1998, wherein the Examiner discusses the teaching of the two references combined to reject Applicants' claims and then asserts, without evidentiary support, that this teaching would have motivated one of skill in the art to combine them "for the express reason that Kahn et al. taught that the vectors were useful for recombinant expression of a protein of interest and Mullenbach et al. illustrate that glutathione peroxidase is a protein of interest." No particular suggestion, teaching, or motivation to combine the references is identified by the Office. No factual findings that might serve to support a proper obviousness analysis are provided. Instead, the Office merely alleges that a general usefulness would have led on of skill in the art to combine the two references to read on the claimed invention. This is not a clear and particular showing, that is, actual evidence, that the claimed invention would have been obvious to one of ordinary skill in the art in view of the teaching of the cited references. Furthermore, even if Kahn would

have provided a general incentive to use adenovirus vectors to express a protein of interest, that general incentive would not have made obvious Applicants' particular result. *Cf. In re Deuel*, 34 U.S.P.Q.2d 1210, 1216 (Fed. Cir. 1995) ("A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out.").

In place of the required evidence supporting the conclusion that one of ordinary skill in the art would have been motivated to combine Kahn and Mullenbach, the Office simply points to Kahn's allegedly general teaching of expressing useful proteins from adenovirus vectors with Mullenbach's work as evidence that glutathione peroxidase is a useful protein for the suggestion to clone DNA encoding glutathione peroxidase into an adenovirus vector. Under similar facts, the Court of Appeals for the Federal Circuit reversed the Office's determination that claims to a chimeric gene were obvious. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Vaeck claimed the following chimera:

1. A chimeric gene capable of being expressed in Cyanobacteria cells comprising:

(a) a DNA fragment comprising a promoter region which is effective for expression of a DNA fragment in a Cyanobacterium; and

(b) at least one DNA fragment coding for an insecticidally active protein produced by a *Bacillus* strain, or coding for an insecticidally active truncated form of the above protein or coding for a protein having substantial sequence homology to the active protein,

the DNA fragments being linked so that the gene is expressed.

20 U.S.P.Q.2d at 1440.

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This claim, and others, were rejected as unpatentable under 35 U.S.C. § 103 based on Dzelzkalns in view of Sekar I or Sekar II and Ganesan. *Id.* at 1441. The primary reference taught a chimeric gene comprising a promoter region effective in a cyanobacterium operably linked to a structural gene encoding chloramphenicol acetyltransferase ("CAT"). The three secondary references collectively taught expression of genes encoding *Bacillus* insecticidal proteins in three bacteria: *B. megaterium*, *B. subtilis* and *E. coli*. *Id.*

In making the rejection, the Examiner admitted that the claimed chimera of Dzelzkalns differed from Vaeck's invention in that the structural gene in the reference encoded CAT while that in the claimed invention encoded an insecticidally active protein. *Id.* As the court states, the Examiner pointed to the three secondary references to cure this deficiency:

However, the examiner pointed out, Sekar I, Sekar II, and Ganesan teach genes encoding insecticidally active proteins produced by *Bacillus*, and the advantages of expressing such genes in heterologous hosts to obtain larger quantities of the protein. The examiner contended that it would have been obvious to one of ordinary skill in the art to substitute the *Bacillus* genes taught by Sekar I, Sekar II, and Ganesan for the CAT gene in the vectors of Dzelzkalns in order to obtain high level expression of the *Bacillus* genes in the transformed cyanobacteria. The examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for the expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the expression of heterologous genes.

Id. at 1441-42. The Board of Patent Appeals and Interferences affirmed the rejection.
Id. at 1442.

The Federal Circuit reversed. *Id.* at 1444. The court held that the PTO had not established the *prima facie* obviousness of the claimed invention because the prior art failed to teach or suggest expression of a chimeric gene encoding insecticidally active protein in cyanobacteria, or convey a reasonable expectation of success in doing so. *Id.* at 1443. The court found no suggestion in Dzelzkalns, the primary reference, of substituting a *Bacillus* structural gene encoding insecticidally active protein for the CAT gene used for selection purposes. According to the Court, "[t]he expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes." *Id.*

To find the instant claims obvious the Examiner applies the same disfavored reasoning asserted by the examiner in Vaeck. That is, it would have been obvious to take Kahn's teaching of adenovirus vectors and substitute for a heterologous gene described therein a DNA encoding glutathione peroxidase as taught by Mullenbach. One of ordinary skill in the art would have been motivated to make that substitution, states the Office, because Kahn teaches that his vectors can be used for expressing useful proteins and Mullenbach's work is evidence that glutathione peroxidase is a useful protein. Wilson asserts that adenoviruses offer certain advantages for gene therapy. Applicants submit that this general incentive would not have rendered their specific invention obvious. *Vaeck* at 1445; *Ex parte Obukowicz*, 27 U.S.P.Q.2d 1063, 1065 (Bd. Pat. App. & Int. 1992) ("The [prior art] statement is of the type that gives only general guidance and is not at all specific as to the particular form of the claimed

invention and how to achieve it. Such a suggestion may make an approach 'obvious to try' but it does not make the invention obvious.").

Under the precedent set forth in *Dembiczak*, as well as the other reasons expressed herein, the Office has failed to establish one of the three requirements for a *prima facie* case of obviousness. The mere fact that references can be combined does not render the resulting combination obvious unless the prior art also suggests the desirability of the combination. M.P.E.P. § 2143.01, *citing In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Here, the desirability of the combination is found only in Applicants' specification. Accordingly, this rejection under 35 U.S.C. § 103(a) is improper and should be withdrawn.

**B. Claims 27, 28, 30, 31, 34-36, 39-41, and 48-50
Are Patentable Over McClelland in View of Mullenbach**

The Office has maintained the rejection of claims 27, 28, 30, 31, 34-36, 39-41, and 48-50 as allegedly unpatentable over U.S. Patent No. 5,543,328 to McClelland *et al.* ("McClelland") in view of Mullenbach.^{2/} (Office action, page 8.) Applicants traverse for the reasons of record, as well as those discussed above.

The asserted teaching of Mullenbach has been discussed. McClelland is cited as disclosing recombinant adenoviral vectors. (Office action mailed January 21, 1998, page 21.) The Office admits that McClelland "does not teach that glutathione peroxidase is a protein of interest." (*Id.*) For this teaching, Mullenbach is relied on, just as in the rejection involving Kahn.

^{2/} Claims 28, 30, 31, and 39 have been canceled. As to these claims, the rejection is moot.

The reasoning offered by the Office to explain why the teaching of these references would have been combined by one of ordinary skill in the art matches the previously discussed rejection:

[I]t would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate cDNA encoding a human or bovine glutathione peroxidase, taught by Mullenbach et al., into the adenoviral vectors and subsequently infected cells taught by McClelland et al. with a reasonable expectation of success as only routine techniques would have been required, and for the express reason that McClelland et al. taught that the vectors were useful for recombinant expression of a protein of interest and Mullenbach et al. illustrate that glutathione peroxidase is a protein of interest.

(*Id.*)

Thus, this rejection suffers the same deficiencies as noted for the rejection over Kahn in view of Mullenbach. For the reasons set forth in reply to that rejection, the Office has not established a *prima facie* case of obviousness. No particular teaching, suggestion, or motivation to combine the teachings of McClelland and Mullenbach has been identified. Accordingly, this rejection is improper and the Office should withdraw it.

**C. Claims 36-38 and 50 Are Patentable Over
McClelland and Mullenbach in view of Akli**

Claims 36-38 and 50 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over McClelland and Mullenbach, and further in view of Akli *et al.*, Transfer of a foreign gene into the brain using adenovirus vectors, *Nature Genetics*, 3:224-28 (1993) ("Akli").^{3/} (Office action, page 8.) Applicants traverse this rejection for the reasons of record and discussed above.

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The rejection is moot as to claim 37, which has been cancelled.

The Office has cited McClelland and Mullenbach as applied to claims 27, 28, 30, 31, 34-36, 39-41, and 48-50. (*Id.*, pages 8 and 9.) It states that this combination of references does not "teach that the DNA of interest could be operably linked to the RSV-LTR promoter or that glial cells could be infected. (Office action mailed January 28, 1998, page 22.) To fill this gap, Akli is cited. (*Id.*) Akli, however, does not cure the deficiencies in the teachings of McClelland and Mullenbach.

As discussed by Applicants, the Office has not proffered any specific evidence that one of ordinary skill in the art would have been motivated to combine the teachings of McClelland and Mullenbach. Akli does not provide this motivation. Akli, according to the Office, merely teaches the use of an RSV-LTR promoter in adenoviral constructs and infection of glial cells by recombinant adenovirus. Hence, for the reasons set forth above, the claims are not *prima facie* obvious over the combined teaching of McClelland, Mullenbach, and Akli. Applicants request reconsideration and withdrawal of the rejection.

SUMMARY

In view of the above remarks, Applicants submit that this application is in condition for allowance. An early and favorable action is earnestly solicited.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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